Facile Syntheses of Cyclophellitol and its (1*R*,6*S*)-, (1*R*,2*S*,6*S*)-, (2*S*)-Diastereoisomers from (−)-Quinic acid

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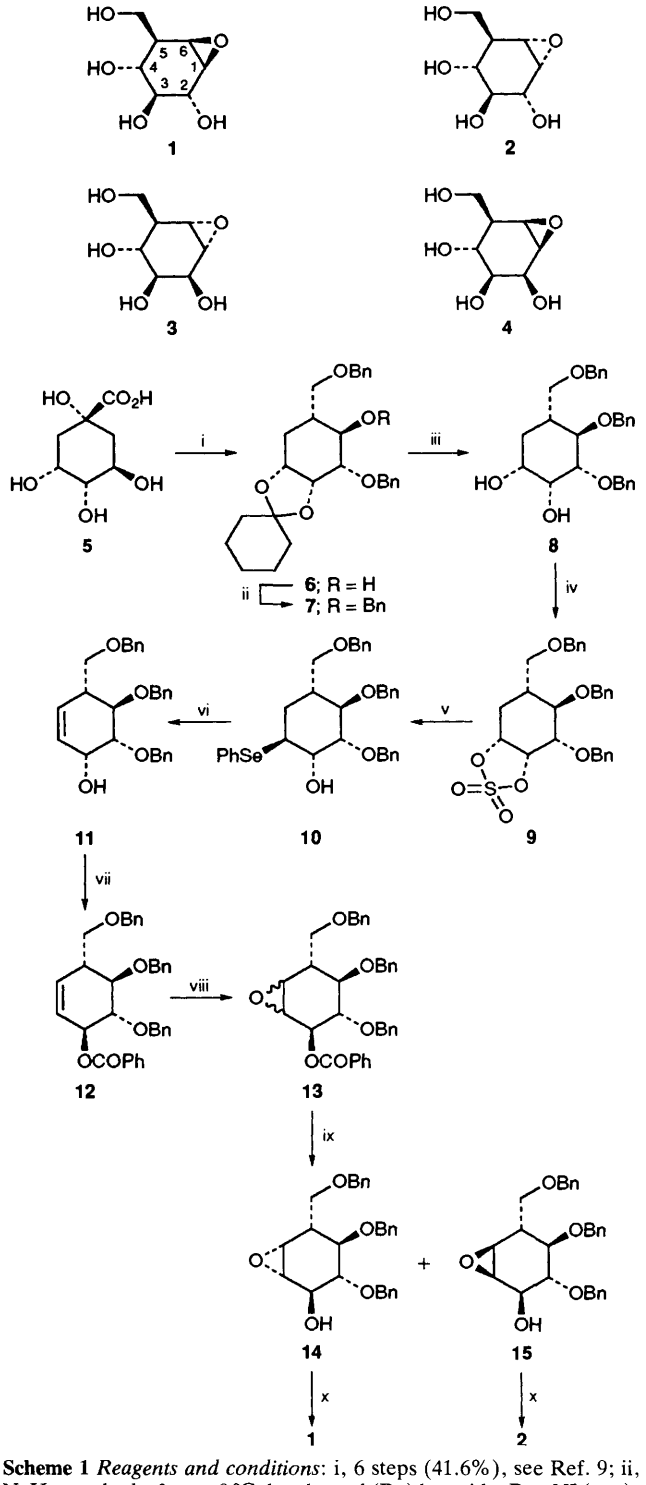
Cyclophellitol and its (1*R*,6*S*)-, (1*R*,2*S*,6*S*)-, (2*S*)-diastereoisomers are constructed from quinic acid involving a regioselective cyclic sulfate ring opening reaction, a regiospecific oxidative elimination, and an epoxidation reaction.

Cyclophellitol {(1*S*,2*R*,3*S*,4*R*,5*R*,6*R*)-5-hydroxymethyl-7-oxabicyclo[4.1.0.]heptane-2,3,4-triol} **1**, isolated from the culture filtrates of mushroom *Phellinus sp.*, has been shown to be a potent inhibitor of β-D-glucosidase.[1] Interests in cyclophellitol have yielded three syntheses starting from L-glucose,[2,3] from L-quebrachitol[4] and from a Diels–Alder adduct.[5] The structure of cyclophellitol **1** corresponds to a pseudo-β-D-glucopyranose whereas its (1*R*,6*S*)-diastereoisomer **2**,† a pseudo-α-D-glucopyranose, has been synthesised from D-galactose and demonstrated to be a specific α-D-glucosidase inhibitor.[3] Along the same vein of reasoning, (1*R*,2*S*,6*S*)- and (2*S*)-diastereoisomers of cyclophellitol, *i.e.* **3** and **4** (pseudo-α- and -β-D-mannopyranose), would be expected to be an α- and a β-D-mannosidase inhibitor, respectively. Indeed, **3** has recently been constructed from D-galactose and displayed α-D-mannosidase inhibitory activity.[6] As part of our programme on the use of quinic acid as a homochiral precursor in organic synthesis, we have already described enantiospecific syntheses of 2-crotonyloxymethyl-(4*R*,5*R*,6*R*)-4,5,6-trihydroxycyclohex-2-enone (COTC),[7] pseudo-β-D-mannopyran-

† It is inappropriate to name this compound as 1,6-*epi*-cyclophellitol because *epi* implies difference in configuration at only one atom.

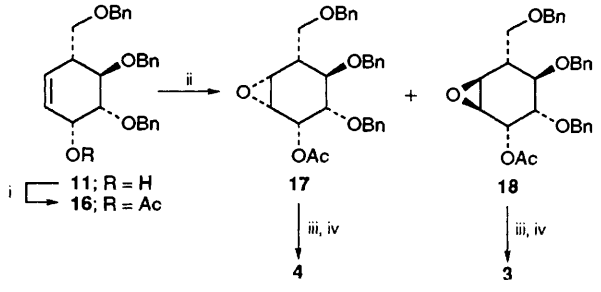
ose, pseudo-β-D-fructopyranose,[8] pseudo-α-D-glucopyranose and pseudo-α-D-mannopyranose.[9] This communication demonstrates further the versatility of this approach in the facile syntheses of **1**, **2**, **3** and **4**.



Scheme 1 *Reagents and conditions*: i, 6 steps (41.6%), see Ref. 9; ii, NaH, tetrahydrofuran, 0 °C then benzyl (Bn) bromide, Bu^n_4NI (cat.), reflux, overnight (82%); iii, CF_3CO_2H, CH_2Cl_2, room temp., 24 h (90%); iv, triethylamine, thionyl chloride, CH_2Cl_2, O °C, 5 min then $NaIO_4$, $RuCl_3$, CCl_4, MeCN, H_2O, 0 °C–room temp., 1 h, (89%); v, diphenyl diselenide, sodium borohydride, EtOH, 0 °C then H_2SO_4, H_2O, (80%); vi, MCPBA, CH_2Cl_2, −40 °C then Pr^i_2NEt, toluene, 80 °C, (72%); vii, benzoic acid, triphenyl phosphine, diethylazodicarboxylate, toluene, 0 °C, 30 min, (93%); viii, MCPBA, CH_2Cl_2, reflux, 48 h, (66%); ix, potassium carbonate (cat.), MeOH, room temp., (95%), (**14**:**15** = 1:2.7); x, H_2, 5% Pd/C, EtOH, room temp., (for **1**, 98%; for **2**, 100%).

The route to cyclophellitol **1** and its (1*R*,6*S*)-diastereoisomer **2** is illustrated in Scheme 1. Our previous work has indicated that quinic acid **5** can be converted readily into the alcohol **6** in six stages with an overall yield of 41.6%.[9] Blocking the free alcohol in **6** as the benzyl ether **7** followed by acid hydrolysis afforded the diol **8**, m.p. 110–112 °C; $[\alpha]_D^{20}$ + 26.3 (*c* 1.2, $CHCl_3$).‡ According to the Sharpless protocol,[10] the diol **8** was transformed smoothly into the cyclic sulfate **9**, m.p. 106–108 °C; $[\alpha]_D^{20}$ + 27.8 (*c* 0.9, $CHCl_3$). Regioselective opening of the cyclic sulfate **9** with selenide anion followed by acid hydrolysis formed the *trans*-diaxial seleno-alcohol **10** as the sole product. Oxidative elimination of **10** *via* the selenoxide occurred regiospecifically[11] away from the hydroxy group, leading to the allylic alcohol **11** as a colourless oil, $[\alpha]_D^{28}$ + 54.3 (*c* 1.3, $CHCl_3$). The configuration of the alcohol in **11** was inverted *via* the Mitsunobu reaction[12] to the β-benzoate **12**, m.p. 54.5–55.5 °C; $[\alpha]_D^{28}$ + 216 (*c* 1.2, $CHCl_3$). Epoxidation of the alkene in **12** with *m*-chloroperbenzoic acid (MCPBA) gave a mixture of inseparable oxiranes **13** which upon debenzoylation provided, after chromatography, the alcohols **14**, m.p. 76.5–78.5 °C; $[\alpha]_D^{23}$ + 111 (*c* 0.4, $CHCl_3$) and **15**, m.p. 112–113 °C; $[\alpha]_D^{28}$ + 86.4 (*c* 0.6, $CHCl_3$) in a ratio of 1:2.7.§ Deprotection of **14** and **15** gave cyclophellitol **1**, m.p. 146–148 °C [lit.,[1] m.p. 149–151 °C]; $[\alpha]_D^{23}$ + 100 (*c* 0.3, H_2O) {lit.,[1] $[\alpha]_D$ + 103 (*c* 0.5, H_2O)} and its (1*R*,6*S*)-diastereoisomer **2**, m.p. 155–157 °C [lit.,[3] m.p. 150–152 °C]; $[\alpha]_D^{23}$ + 83.3 (*c* 0.3, H_2O){lit.,[3] $[\alpha]_D$ + 80 (*c* 0.4, H_2O)}.¶

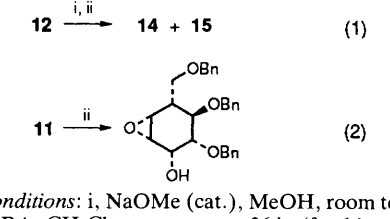
The formation of (1*R*,2*S*,6*S*)- and (2*S*)-diastereoisomers of cyclophellitol, **3** and **4**, is shown in Scheme 2. Acetylation of **11** afforded the acetate **16** in which the alkene moiety was epoxidised to give the readily separable oxiranes **17**, m.p. 59–61 °C; $[\alpha]_D^{24}$ + 4.8 (*c* 2.7, $CHCl_3$), and **18**, $[\alpha]_D^{24}$ + 14.3 (*c*



Scheme 2 *Reagents and conditions*: i, $(MeCO)_2O$ (Ac_2O), pyridine, *N*,*N*-dimethylaminopyridine (cat.), CH_2Cl_2, room temp., 24 h (96%); ii, MCPBA, CH_2Cl_2, reflux, 42 h, (77%, **17**:**18** = 1:1.2); iii, potassium carbonate (cat.), MeOH, room temp., 24 h; iv, H_2, 5% Pd/C, EtOH, room temp., (two steps, for **3**, 86%; for **4**, 81%).

‡ All new compounds gave satisfactory analytical and spectral data.

§ Debenzoylation of **12** formed the corresponding allylic alcohol which was epoxidised to give **14** and **15** in a ratio of 5:95 [eqn. (1)]. Epoxidation of **11** gave **19** as the sole product [eqn. (2)].



Reagents and conditions: i, NaOMe (cat.), MeOH, room temp., 12 h, (94%); ii, MCPBA, CH_2Cl_2, room temp., 36 h, (for **14** and **15**, 70%; for **19**, 95%).

¶ ^{13}C NMR data (62.5 MHz, D_2O, dioxane was used as an internal reference at δ 67.4): for **1**, δ 44.3, 56.8, 56.9, 61.4, 67.8, 71.7, 77.1; for **2**, δ 45.0, 55.8, 58.2, 61.3, 70.4, 72.1, 74.0; for **3**, δ 45.3, 55.6, 56.6, 61.6, 66.7, 68.0, 71.2; for **4**, δ 44.8, 54.4, 56.9, 61.8, 66.4, 66.7, 73.2.

2.0, $CHCl_3$), in a ratio of 1:1.2.§ Deprotection of **17** and **18** yielded **3**, m.p. 129–131 °C (lit.,[6] oil]; $[\alpha]_D^{23}$ −39.5 (*c* 0.9, H_2O){lit.,[6] $[\alpha]_D^{25}$ −76 (*c* 0.1, H_2O)} and 2-*epi*-cyclophellitol **4**, m.p. 148–150 °C; $[\alpha]_D^{24}$ + 7.0 (*c* 0.4, H_2O).¶

The present approach to cyclophellitols from quinic acid is flexible and versatile and thus opens routes for facile syntheses of not only other diastereoisomeric pseudo-anhydropyranoses but also their aziridine analogues. Research in this direction is in progress.

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